detectable moieties (e.g., fluorescent dyes). The detectable moiety may be provided by impregnating or coating the bead, or conjugating the moiety (either directly or indirectly) to the surface of the bead. The encoding can take place during or after manufacture of the bead. For convenience, optically detectable moieties will be referred to herein as dyes, without intending any limitation thereby. The identity of the dyes may be varied, and beads may incorporate multiple different dyes. The concentration(s) of the dye(s) may also be varied, resulting in different intensity levels. For example, with three colors provided at 10 different concentrations (intensity levels), 1000 different combinations are obtained. Using this scheme it is possible to encode and subsequently identify 1000 different populations of beads (e.g., beads to which any of 1000 different probes are attached). Numerous suitable dyes are known in the art, and beads incorporating such dyes are commercially available. Fluorescent or luminescent labels that can be used include, but are not limited to, fluorescent lanthanide complexes, including those of europium and terbium, fluorescein, rhodamine, tetramethylrhodamine, eosin, erythrosin, coumarin, methyl-coumarins, pyrene, malachite green, stilbene, Lucifer Yellow, Cascade Blue, Texas Red, FITC, Cy3, Cy5, etc. Such labels and others are described in Mason, W. (ed.) and Mason, B., Fluorescent and Luminescent Probes, Academic Press: San Diego, 1999, in *Handbook of Fluorescent Probes and Research Products* (8th Ed.), Molecular Probes, Inc., and at http://www.probes.com. In addition to the aforementioned molecules, fluorescent nanocrystals referred to as quantum dots may be used to encode the beads. Fluorescent quantum dots consist of a core of a cadmium selenide (CdSe) nanocrystal ranging in diameter from approximately 18 Å to 70 Å, which may be wrapped in a shell of zinc sulfide. The use of quantum dots to label and distinguish between populations of microbeads is described in Han, M., et al., "Quantum-dot-tagged microbeads for multiplexed optical coding of biomolecules", *Nat. Biotechnol.,* 19:631-635, 2001. When multiple dyes or other fluorescent, luminescent, or otherwise optically detectable moieties are used, it is important to ensure that they are distinguishable, e.g., that they absorb and/or emit light at sufficiently different wavelengths to be distinguishable by the detection means employed.

[0169] A second strategy for encoding and decoding is to use a set of hybridization tags. These tags are nucleic acid molecules (encoding tags) whose identity can be determined by hybridization to nucleic acid molecules (decoding tags) having a substantially complementary sequence. By attaching one or more hybridization tags to a particular population of beads (i.e., a population of beads bearing a particular probe), the identity of the bead can be determined by performing hybridization using the decoding tags, which are typically labeled (e.g., with a fluorescent dye) to allow their subsequent detection. As an example, with six different hybridization tags one can obtain 1+6+15+20+15+6+1=64 different combinations and thus encode **64** different populations of beads (assuming between 0 and 6 different hybridization tags are assigned to each bead population). Hybridization tags may range in length from several nucleotides to 50 or more. Tags ranging from approximately 10 to approximately 25 nucleotides in length may be particularly appropriate. It will be appreciated that a greater number of nucleotides allows for more different populations of beads to be encoded but adds to the complexity of synthesis. Methods for attaching nucleic acids to beads are well known in the art and are discussed further in the Assays section below.

[0170] In a typical experiment groups of beads are prepared and various combinations of hybridization tags and probes are bound to the beads in each group. Then a pool of beads is formed, containing a mixture of the various populations. The sample to be interrogated can then be hybridized to the beads in solution or after arraying on the chip. Decoding is performed by adding complements of the six hybridization tags (i.e., the decoding tags) while the beads remain trapped on the chip. This can be done serially, with detection after each hybridization. A more efficient approach is to perform the hybridization in one step, i.e., using a mixture of decoding tags with a different dye attached to each different decoding tag. In this case, the combination of colors reveals the identity of the bead by decoding the combination of tags it contains. The target(s) in the sample are labeled using a different method or a different dye to that used to label the decoding tags. Interaction of a probe with a target (e.g., hybridization of a DNA probe to a complementary nucleic acid in the sample) is revealed by detecting the label specific to target.

[0171] Instead of, or in addition to, employing hybridization as a method of decoding nucleic acid tags, direct sequencing of the tags or probes attached to a bead may be performed. For instance, one can decode the tag or probe sequence on the bead and consequently the bead by sequencing the tag or probe on the bead to reveal the identity of the tag or probe. By directly sequencing the probe the need for employing encoding scheme is avoided because the sequence itself reveals the identity of the probe. With mini-sequencing, the particles do not have to be pre-labeled with a detectable material for decoding. Using mini-sequencing, for example, the DNA sequence surrounding a polymorphism provides the ability to identify the DNA fragment.

[0172] Any appropriate method of on-bead sequencing may be used. One such method is pyrosequencing. In a typical pyrosequencing process, complementary nucleotides are sequentially added to a single-stranded DNA. With each addition, pyrophosphate is released in an amount which is characteristic of the nucleotide being added. ATP sulfurylase quantitatively converts pyrophosphate to ATP in the presence of adenosine 5' phosphosulfate. This ATP drives a luciferase mediated conversion of luciferin to oxyluciferin that generates visible light in amounts that are proportional to the amount of ATP. The light produced in the luciferase-catalyzed reaction can be detected by a detection device such as a charge coupled device or the above-described photodetectors. Various other enzymatic methods are known. Pyrosequencing technologies are described in greater detail at "http:/www.pyrosequencing.com/documents/about/tech.html" and in Ronaghi, et al., *Science,* 281:363, 1998.

[0173] Conservative calculations and also, experiments indicate that a template density of 1000 molecules/μm^2 will yield enough pyrosequencing photons to give a signal to noise greater than 10:1 with a cooled, high-efficiency, unamplified CCD camera. The magnetic beads can easily be coupled to DNA probes at an effective density of 10,000 molecules/μm^2 on each bead. This should easily be detectable with a standard CCD setup.